REMARKS

Claims 12-73 are pending in the application. Claims 12-62 are under active consideration. Claims 12, 16, 17, 24, 25, 27, 30, 31, 42, 53, 59, and 62 are amended as described herein below. New claims 63-73 have been added. Support for the amendments and new claims can be found throughout the specification and in the original claims. Therefore, no new matter has been added by way of claim amendments.

Claims 12, 16, 17, and 42 have been amended to provide a sequence identifier for the amino acid sequence of IL-2 (SEQ ID NO:1). A new Sequence Listing setting forth the recited sequence is filed concurrently herewith. This sequence is disclosed in Fig. 15b of U.S. Patent No. 4,518,584, which patent was incorporated by reference in the present specification, for example, at page 17, line 21. In addition, the first paragraph on page 29 is amended to include the sequence identifier, SEQ ID NO:1, in reference to the IL-2 mutein aldesleukin. No new matter is added by way of these amendments to the specification or by way of presentation of this Sequence Listing. The Examiner is respectfully requested to enter the Sequence Listing and these amendments to the specification.

In order to expedite prosecution, claims 12, 16, 17, and 42 have been amended to recite biologically active variants of IL-2 that activate NK cells. By this amendment, Applicants expressly do not disclaim equivalents of the invention, which could include IL-2 variants having biological activities in addition to activating NK cells. Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Support for this amendment can be found in the specification, for example, at page 12, lines 20-21; page 27, lines 7-14; page 32, lines 13-14; and page 34, lines 9-17. Accordingly, the specification provides adequate support for the amendment. Entry of this amendment is respectfully requested.

In addition, claims 12, 16, 17, and 42 have been amended to recite variants of IL-2 that comprise amino acid sequences having at least 90% sequence identity to SEQ ID NO:1. Support for this amendment can be found in the specification, for example, at page 14, lines 11-14. Accordingly, the specification provides adequate support for the amendment. Entry of this amendment is respectfully requested.

Claims 12, 16, 17, and 42 have also been amended to recite that the "anti-HER2 antibody or fragment thereof binds to the extracellular domain of the HER2 receptor protein." Support for

this amendment may be found throughout the specification, for example, on page 21, lines 23-25. Accordingly, claims 24 and 30, which directly or indirectly depend from claim 12, have been amended to remove the limitation regarding the ability of the antibody fragment to bind to the HER2 receptor protein. Claims 25 and 31 have been amended to remove the recitation of "human form." No new matter is added by way of these amendments.

New claims 63-73 are drawn to methods of treating a subject for a cancer using humanized 4D5 or 520C9 antibodies. Entry of the new claims is therefore respectfully requested.

The claim amendments and new claims were not presented earlier as Applicants earnestly believed the previously presented claims recited patentable subject matter. The Examiner is respectively requested to enter these claim amendments and new claims to further prosecution or to place the application in better condition for appeal.

Amendments to the specification have been made at pages 5, 30, and 36 to identify LabCorp™ and Benadryl™ as registered trademarks. These amendments were made to correct the use of registered trademark designations. The specification has also been amended at pages 2, 27, 28, 32, 34, and 35 to remove references to nonessential information contained in the CALGB 9661 Protocol. The specification has been amended at page 28, line 23, to remove an obvious typographical error. No new matter has been added by way of these amendments.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Objections to the Specification

The specification is objected to because of references to "the CALGB 9661 Protocol." The specification has been amended to remove those statements wherein a referral is made to the CALGB Protocol 9661 for nonessential information. Applicants respectfully submit that the material in this reference to which these statements refer is not essential for satisfaction of the requirements for patentability; therefore, the CALGB Protocol 9661 does not need to be incorporated into the specification. As set forth in M.P.E.P. § 608.01(p),

> Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications however, hyperlinks and/or other forms of browser executable code cannot be incorporated by reference. See MPEP § **608.01.** Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

The application as filed is complete in itself. The phase II clinical trial is described in the specification in Example 1 at pages 28-38. No further details from the CALGB Protocol 9661 are necessary to provide support for the claimed subject matter of the invention; therefore the CALGB Protocol 9661 need not be incorporated into the specification. Applicants respectfully submit that this objection is therefore obviated.

The specification is further objected to for the use of improperly demarcated trademarks. The specification has been amended to identify LabCorp™ and Benadryl™ as registered trademarks, therefore obviating this objection.

New Matter and Written Description Rejections under 35 U.S.C. § 112, first paragraph

Claims 25 and 31 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Final Office Action, page 4). In particular, the Final Office Action alleges that the limitation "human form of a murine antibody" is not supported by the original disclosure (Final Office Action, page 5). The Final Office Action further alleges that "the patent does not teach 'a human form' of the murine monoclonal antibody; rather, it teaches humanized versions of such antibodies can be made. Therefore, with regard to claims 25 and 31, because neither a humanized antibody nor a 'human antibody' would be understood to be equivalent of 'a human form of a murine antibody', the description of this subject matter is too inadequate to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention." (Final Office Action, page 10).

Claims 25 and 31, as currently amended, recite a humanized or chimeric form of a murine antibody. Support for chimeric and humanized murine antibodies can be found in the

specification, for example, at page 22, lines 11-16. Applicants submit that no new matter is added by the claim as currently amended.

For at least these reasons, withdrawal of the new matter and written description rejections under 35 U.S.C. § 112, first paragraph is respectfully requested.

Written Description Rejection under 35 U.S.C. § 112, first paragraph

Claims 12-27 and 29-32 have been rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of an adequate written description. In particular, the Final Office Action alleges that "the amino aid sequence of IL-2 is not disclosed (Office action mailed March 14, 2003, page 6, paragraph 2); so, the comparison recited in the claims cannot be made" (Final Office Action, page 6). The Final Office Action further alleges that "the genus of IL-2 and variant thereof is exemplified by the disclosure of a single non-reperesentative species, namely Proleukin™ (aldesleukin) which is a recombinant human IL-2 mutein; see, e.g., the specification at page 29, lines 2-10. The disclosure of this one species of molecules is not deemed representative because the specification has not defined the structural and functional features of Proleukin™ that uniquely describe the members of the genus of IL2 and variants thereof, as a whole, such that one skilled in the art could immediately discern at least most of its members." (Final Office Action, page 8.) The Final Office Action further alleges that "the skilled artisan cannot accurately and reliably predict whether a protein having as little as 70% amino acid sequence identity with another protein will have or retain any particular function of the later" (Final Office Action, page 9). Applicants respectfully traverse the rejection on the following grounds.

The fundamental factual inquiry in written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. *See, e.g., Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Determining whether the written description requirement is satisfied is a question of fact and the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976). It is not necessary that the application describe the claimed invention *in ipsis verba.* Rather, all that is required is that the specification reasonably

convey possession of the invention. *See, e.g., In re Lukach,* 169 USPQ 795, 796 (CCPA 1971). Finally, determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. *See, e.g., In re Lange,* 209 USPQ 288 (CCPA 1981).

Furthermore, the Patent Office's own guidelines on written description are clear -- the written description requirement is highly fact-dependent and there is a strong presumption that an adequate written description of the claimed invention is present at the time of filing:

> [t]he description need only describe in detail that which is new or not conventional. This is equally true whether the claimed invention is a product or a process. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics. ... A "representative number of species" means that the species that are adequately described are representative of the entire genus. ... What constitutes a "representative number" is an inverse function of the skill and knowledge of the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. ... Description of a representative number of species does not require the description be of such specificity that it would provide individual support for each species that the genus embraces. (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099, emphasis added).

Simply put, there is absolutely **no** requirement that Applicants exemplify (or reduce to practice) every sequence falling within the scope of the claims in order to adequately describe the methods using IL-2 variant polypeptides as claimed. Rather, the test is whether the specification contains sufficient disclosure regarding structural and functional characteristics of the recited sequences to satisfy the written description requirement. In the pending case, the specification as filed more than adequately describes the structure and function of the recited IL-2 polypeptides.

As amended, independent claims 12, 16, 17 and 42 recite methods using IL-2 polypeptides comprising the sequence of SEQ ID NO:1 or variants thereof having a sequence

with 90% identity to the sequence of SEQ ID NO:1. Applicants note that the amino acid and nucleotide sequences of IL-2 were well known to one of skill in the art at the time of filing of the instant application and that the sequence of SEQ ID NO:1, in particular, was disclosed in U.S. Patent No. 4,518,584, which was incorporated by reference into the instant specification (see specification at page 17, line 21). Applicants have amended the claims to recite IL-2 polypeptides comprising the sequence of SEQ ID NO:1 or variants thereof and have, accordingly, submitted a Sequence Listing setting forth the sequence of SEQ ID NO:1.

Thus, the claims, as currently amended, clearly recite both the structure (sequence of SEQ ID NO:1 or variants 90% identical to SEQ ID NO:1) and function (activate NK cells) of the recited IL-2 polypeptides. Although, the Final Office Action states that a skilled artisan could not readily distinguish a human variant of IL-2 from a non-human variant of IL-2 (Final Office Action, page 8); there is no such requirement. The claims require only that the variant polypeptide comprise a sequence having at least 90% sequence identity to SEQ ID NO:1 and activate NK cells. Therefore, when properly construed, it is plain that only polypeptide sequences having the recited structure and function are encompassed by the pending claims. The written description requirement is satisfied because the specification describes sufficient structural and functional characteristics of the claimed molecules.

The specification as filed fully describes the claimed subject matter. The specification describes, in detail, IL-2 polypeptides and variants thereof (see specification, *e.g.*, page 17, lines 1-27 and Example 1). Further, the art provides substantial guidance regarding the preparation and use of IL-2 variants (see specification, *e.g.*, page 16, lines 26-30). In particular, the specification describes the IL-2 variant Proleukin®, which differs from native IL-2 sequence in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by a serine residue (see specification at page 29, lines 3-7). In addition, the sequences of numerous IL-2 polypeptides and variants are described in various publications, patent applications, and issued patents cited in the specification at page 17, lines 12-14 and lines 15-27, all of which are incorporated by reference. With regard to percent identity, the specification clearly describes how to determine percent identity between polypeptides, for example, in the text beginning on line 17 of page 14. Performing such alignments is routine and conventional. Any polypeptide exhibiting the requisite 90% identity can be readily evaluated for biological activity in activating

NK cells as described, for instance, in the specification as filed (See, *e.g.,* Example 1 at pages 26-28 and page 34, lines 9-17).

Applicants direct the Examiner's attention to the Patent Office's own guidelines regarding the written description requirement. Example 14 of the Patent Office's "Synopsis of Application of Written Description Guidelines" is clear that a **single** disclosed species may be representative of a "product-by-function" genus when all members exhibit structural identity to a reference compound (here, SEQ ID NO:1) and when an assay is provided for identifying all variants having the claimed activity (such as detailed in Example 1). The Examiner has failed to point out any substantive distinctions between Example 14 and the recitations in the present claims in the Office Action. In fact, Example 14 of the Synopsis is completely on point. Example 14 is reproduced below:

> **Claim**:
> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A⇒B.
>
> **Analysis:**
> ... The procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art. ....
>
> There is actual reduction to practice of a single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The **single species disclosed** is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> **Conclusion:** The disclosure meets the requirements of 35 U.S.C. § 112, first paragraph as providing adequate written description for the claimed invention. (Example 14, emphasis added.)

Like Example 14, applicants in the pending case have provided a limit to the structural identity (now 90% identity), a specified activity of the variants (activates NK cells) and methods for identifying constructs exhibiting the specified activity (See, *e.g.*, Example 1 of the application). Therefore, as in PTO Example 14, the multiple species disclosed in the application are representative of the genus as a whole.

Accordingly, one of skill in the art would conclude applicant was in possession of the necessary common attributes possessed by the members of the genus, and it is clear that, as concluded in PTO Example 14, the present application provides adequate written description for the substance of claims 12, 16, 17, and 42.

The Cases Cited are Not Applicable

Furthermore, the Office's reliance on *Colbert v. Lofdahl, Regents of the Univ. Calif. v. Eli Lilly*, *Fiers v. Revel* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* is misplaced. The written description requirement of section 112 is highly fact dependent and the claims, disclosure and state of the art in *Colbert, Eli Lilly, Fiers,* and *Amgen* are entirely different from those in the case at hand. Indeed, the specification and claims at issue in *Colbert, Eli Lilly, Fiers,* or *Amgen* were defective because they were devoid of any structure (sequence) disclosure. In contrast, Applicants' specification as filed and the pending claims contain and recite ample structural and functional characteristics.

Furthermore, the Federal Circuit's holdings in *Colbert, Eli Lilly, Fiers,* or *Amgen* in no way necessitate that the claims be limited in scope to those sequences disclosed in SEQ ID NOs. Indeed, in *Fiers v. Revel*, the Federal Circuit indicated that, although disclosure of a method of isolating DNA did not adequately describe the DNA, the DNA itself may be properly defined by one or more of the following parameters: "structure, formula, chemical name or physical properties." Thus, it is possible that DNA can be entirely described by its physical properties, *i.e.* by function. Again, Applicants' disclosure and claims include both structure and physical properties and, accordingly, the cases cited by the Office are not relevant to the case at hand.

The present application has a priority date of May 15, 2000. Much has happened in the development of recombinant DNA technology in the 18 or more years from the time of filing of

the applications involved in *Colbert, Eli Lilly, Fiers,* and *Amgen* and the present application. For example, the technique of polymerase chain reaction (PCR) was developed. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

For at least the above reasons, withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Enablement Rejection under 35 U.S.C. § 112, first paragraph

Claims 12-62 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an enabling disclosure commensurate in scope with the claims. In particular, the Final Office Action alleges that "the specification, while being enabling for a method for treating a patient diagnosed with breast cancer that overexpresses HER2 comprising administering to the patient a therapeutically effective amount of Herceptin™ in combination with a therapeutically effective amount of Proleukin™, does not reasonably provide enablement for a method for treating a subject having a cancer that is characterized by overexpression of HER2" (Final Office Action, page 10). The Final Office Action further alleges that "[a]s evidenced by the teachings of Skolnick et al. (of record), the art of protein chemistry is highly unpredictable; apart from disclosing the use of Proleukin™, the specification does not exemplify the use of any other member of the genus of IL-2 molecules and variants thereof to which the claims refer" (Final Office Action, page 11). In addition, the Final Office Action alleges that the specification fails to teach the amino acid sequence of IL-2 or the amino acids of the amino acid sequence of IL-2 that can be replaced or deleted, or between which amino acids additional amino acids can be inserted, or by which other amino acid replacements can be made, so the variant retains the activity of human IL-2 (Final Office Action, page 11). The Final Office Action also alleges that antibodies that bind to the intracellular domain of HER2 are not disclosed in the specification (Final Office Action, page 12). The Final Office

Action further alleges that "[t]he specification has not provided the guidance and direction necessary to enable the skilled artisan to distinguish which anti-HER2 antibodies can or cannot be used effectively, but moreover, as evidenced by U.S. Patent No. 5,772,997 (of record), it appears only antibodies that bind a few particular epitopes of the extracellular domain of HER2 are capable of inhibiting the growth of tumor cells (Final Office Action, page 13). The Final Office Action further alleges that "the skilled artisan could not reasonably expect to use the claimed invention to treat types of cancer, other than breast cancers overexpressing HER2, without first determining whether the antibody is capable of inhibiting the growth of the other types of cancer" (Final Office Action, page 13). Applicants respectfully traverse the rejection on the following grounds.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Undue experimentation is not required to practice the claimed invention because the claims are enabled throughout their scope and, in addition, the references cited by the Examiner do not in any way establish unpredictability. When the *Wands* factors are considered, it is clear that the specification as filed fully enables the pending claims throughout their scope.

IL-2 Variants

The Examiner has asserted that the claimed methods use a large genus of IL-2 polypeptides and that a representative number of species of that genus are neither contemplated nor taught in the specification. (Final Office Action, pages 11-12). This is not a correct application of the law. Applicants are under no legal obligation to teach each and every member

of a claimed genus. Rather, for a claimed genus, representative examples together with a statement applicable to the genus as whole is sufficient to establish enablement if the skilled artisan would expect the claimed genus could be used in the manner set forth. *See, e.g.,* U.S. Patent and Trademark Office's Training Materials on Enablement, p. 29. The present record is replete with representative examples and statements applicable to the genus as a whole.

As mentioned above, Applicants have amended independent claims 12, 16, 17, and 42 to recite methods using IL-2 polypeptides comprising the sequence of SEQ ID NO:1 or variants thereof having a sequence with 90% identity to the sequence of SEQ ID NO:1. Applicants have also submitted a Sequence Listing setting forth the sequence of SEQ ID NO:1, which was disclosed in U.S. Patent No. 4,518,584, and incorporated by reference into the present specification.

Representative examples of sequences falling within the scope of the claims are provided in the specification (see, *e.g.*, page 17, lines 15-25). In addition to these representative examples, statements applicable to the genus as whole are provided throughout the specification, for example, on pages 14-15 *et seq.* where it is noted how to determine sequences falling within the requisite percent identity. At the time of filing, determining sequence identity was utterly routine. The specification also provides guidance (see specification, *e.g.,* at pages 16-17) regarding the preparation and use of IL-2 polypeptide variants. Substantial guidance is also given in regards to determining whether an IL-2 polypeptide activates NK cells, as required by the claims. (See specification, *e.g.,* at page 12, line 29 through page 13, line 2 and Example 1). Thus, the specification provides ample guidance as to identification, generation, and testing of IL-2 polypeptides that can be used in the claimed invention.

The Examiner has cited Skolnick et al. (*Trends in Biotechnology* 18:34-39, 2000) as allegedly establishing the unpredictability of the art as relevant to the claimed invention. Specifically, the Office Action reasserts that the reference of Skolnick et al. demonstrates that it would require undue experimentation to determine which IL-2 variants retain the function of Proleukin™ and could be used in the claimed methods. (Final Office Action, pages 11). However, upon careful review, it is clear that the reference of Skolnick et al. is <u>not</u> relevant to the claimed subject matter.

As stated previously, Skolnick et al. merely demonstrate in proteins unrelated to IL-2 that mutations may result in non-functional proteins. IL-2 is a well-known, well-characterized protein, and the art provides substantial guidance regarding the preparation of biologically active IL-2 polypeptides and variants thereof. Moreover, numerous representative examples of IL-2 variants having biological activity comparable to native IL-2 have been described previously. See specification, for example, at page 17, lines 15-27 and references cited therein. Methods for mutagenesis and nucleotide sequence alterations are also well known in the art. See specification, for example, at page 13, lines 21-31. One of skill in the art can routinely produce IL-2 polypeptides and variants thereof, and IL-2 variants that do not activate NK cells are not encompassed by the claims.

Further, it is well settled that time-consuming or expensive experimentation is **not** undue if it is routine. (See, *e.g.,* PTO Training Manual on Enablement, pages 30-31, citing *United States v. Telectonics Inc.,* USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied* 490 U.S. 1046 (1989) holding the disclosure of a single exemplified embodiment and a method to determine other embodiments was enabling, even in the face of evidence that determining additional embodiments might require 6-12 months of effort and cost over $50,000). Thus, the possibility of generating inoperative embodiments, allegedly established by the cited references discussed above, is not relevant to the claimed invention.

Furthermore, the presence of inoperative embodiments does not necessarily render a claim nonenabled. *See, e.g.,* MPEP § 2164.08(b); and *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219, CCPA 1976. The test of enablement is not what is predictable *a priori*, but what the specification teaches the skilled practitioner in regard to the claimed subject matter. Thus, not every species (or even a majority of species) encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219, CCPA 1976. The notion that one of ordinary skill in the art must have reasonable assurances of obtaining positive results on every occasion has been emphatically rejected. *Angstadt* at 219. So long as it is clear that some species render the claims operative, the inclusion of possible inoperative species cannot invalidate the claim under paragraph 1 of 35 U.S.C. §112. *See, also, In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988.

In the pending case, Applicants again note that every single polypeptide species exhibiting 90% identity to SEQ ID NO:1 can be determined *a priori* and, as such, the entire genus of polypeptides exhibiting 90% identity to these sequences is enabled by the specification as filed.[1] Thus, there are no inoperative "structural" embodiments encompassed by the claims and, as such, the specification clearly enables the structures (sequences) recited in the claims.

Moreover, as set forth in the case law described above, the possibility that there may be some inoperative "functional" embodiments (*e.g.*, some of the polypeptides may not activate NK celles) does not render the specification nonenabling because the specification clearly teaches how to test for NK cell activation and indicates that such testing is utterly routine. See specification, for example, at Example 1 at page 34, lines 9-17. Routine experimentation, as would be required to determine if an embodiment falls within the "functional" scope of the claims, is not undue experimentation.

Thus, not only does the claim language itself exclude inoperative embodiments, namely any and all polypeptides that do not activate NK cells, the experimentation needed to identify inoperative embodiments is not undue. Accordingly, the presence of potentially inoperative functional embodiments cannot form grounds for rejecting the pending claims as allegedly nonenabled.

Anti-HER2 Antibodies

With regard to HER2 antibodies, claims 12, 16, 17, and 42 have been amended to recite that the "anti-HER2 antibody or fragment thereof binds to the extracellular domain of the HER2 receptor protein." The Final Office Action alleges that Lewis *et al.* and Skolnick *et al.* show that the skilled artisan cannot predict which anti-HER2 antibodies can be used to treat cancer, since only certain antibodies can be used effectively to inhibit the growth of cancer cells. The Final Office Action also states that Lewis *et al.* show that the skilled artisan cannot accurately and

[1] Applicants also direct the Examiner's attention to Example N:DNA of the Patent Office's "Training Materials for Examining Patent Applications with respect to 35 U.S.C. § 112, First Paragraph -- Enablement -- Chemical/Biotechnical Applications," which states that even with a very large genus of sequences (at least 1.26×10^{21}), undue experimentation is not required to determine all members of the genus because "each embodiment can be readily identified using the genetic code, synthesized using conventional methods, and used in the manner taught in the specification." see, page N-4.

reliably predict which types of cancer can or cannot be treated on the basis of the level of expression of HER2, that the determination can only be made empirically, and that additional undue experimentation would be required before the claimed invention could be practiced. Applicants respectfully disagree with this conclusion.

Just because a determination must be made empirically does not mean that undue experimentation is required. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom.; *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. Moreover, "all that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims." M.P.E.P. § 2164.08, citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicants respectfully point out that it is the burden of the Examiner to show why one skilled in the art would consider the amount of experimentation undue.

The Examiner has merely pointed out that some testing will need to be done, not that this testing is undue. As methods for determining whether an anti-HER2 antibody is capable of inhibiting the growth of tumor cells are well known in the art, and as all that is required by one skilled in the art is to obtain an anti-HER2 antibody and test its ability to inhibit cancer cell growth, Applicants have enabled the use of anti-HER2 antibodies in the methods of the present invention. It is not necessary to determine which epitopes of HER2 the anti-HER2 antibodies bind to; it is merely necessary to determine if the antibodies inhibit cancer cell growth.

Applicants therefore submit that the rejections of claims 12-62 on the grounds that some antibodies that bind to HER2 have been shown to promote tumor growth, and that the claims are broadly drawn to methods for treating cancer while the specification only discloses working examples with breast cancer patients, are not suitable grounds for establishing undue experimentation to practice the claimed invention. Accordingly, this aspect of the enablement rejection should be withdrawn.

The Examiner further alleges that the greater effectiveness of the combination of Herceptin™ and Proleukin™ depends on the ability of the antibody to mediate ADCC, and that the claims are not presently limited to the use of a combination that is known to be effective. However, the Federal Circuit has held "[t]he enablement requirement is met if the description enables *any* mode of making and using the claimed invention." *Engel Industries Inc. v. The Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991), emphasis added. See also, *Johns Hopkins Univ. v. Cellpro, Inc.*, 47 USPQ2d 1705 (Fed. Cir. 1998) and *Durel Corp. v. Osram Sylvania Inc.*, 59 USPQ2d 1238 (Fed. Cir. 2001).

In this case, Applicants have disclosed the use of human and chimeric forms of the monoclonal antibodies 4D5 and 520C9. Accordingly, claims 12-62 meet the enablement requirement set forth by the Federal Circuit in *Engel*, *Johns Hopkins*, and *Durel*, because the specification enables one of skill in the art to use the methods recited in the claims.

Availability of 4D5 and 520C9 Antibodies

In addition, claims 25, 31, 52, 55, 58, and 61 have been rejected under 35 U.S.C. §112, first paragraph, as nonenabled. The Office asserts that the hybridomas producing the 4D5 and 520C9 antibodies are required to practice the claimed invention and therefore "must be known and readily available to the public or obtainable by a repeatable method set forth in the specification" (Final Office Action, page 17). The Office invites applicants to deposit the hybridomas in order to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. However, applicants submit that no deposit is necessary.

MPEP §2404.01 states:

> In an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention. To avoid the need for a deposit on this basis, the biological material must be both known and readily available - neither concept alone is sufficient. A material may be known in the sense that its existence has been published, but is not available to those who wish to obtain that particular known biological material. Likewise, a biological material may be available in the

sense that those having possession of it would make it available upon request, but no one has been informed of its existence.

The 4D5 and 520C9 antibodies are **both** known and readily available to the public as required by MPEP §2404.01. In particular, there are numerous publications referring to the 4D5 and 520C9 antibodies. A list of but some of these publications from a search of the NCBI database is appended to this response at Appendix A. Moreover, U.S. Patent Nos. 5,677,171 and 6,054,561 describe the production of these antibodies. Additionally, the antibodies are indeed commercially available. Applicants have provided evidence that the hybridomas producing the monoclonal antibodies 4D5 and 520C9 are readily available from the ATCC (see the ATCC Catalog product descriptions for the 4D5 and 520C9 antibodies attached as Appendix B). In addition, Herceptin®, a humanized form of the 4D5 antibody is readily available from Genentech (see web pages describing Herceptin attached as Appendix C). Accordingly, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

For at least the above reasons, withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. §§ 102 and 103

Claims 12-19, 24, 26-28, 30, 32-40, 42-47, and 51-62 stand rejected under 35 U.S.C. §102(b) as being anticipated by, or in the alternative, under §103(a) as being obvious over U.S. Patent Nos. 4,863,726 (hereinafter the '726 patent) or 4,894,227 (hereinafter the '227 patent). In particular, the Final Office Action alleges that "if the prior art is not clearly anticipatory of the claimed invention, particularly since the prior art does not explicitly teach that a therapeutically effective dose of IL-2 is the range of about 0.5 to about 4.0 mIU/m^2 or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg, any necessary or appropriate modification of the methods disclosed by the prior art, which would be amply guided by the supporting disclosures, would have been obvious to the ordinarily skilled artisan at the time of the invention" (Final Office Action, pages 20-21). Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference(s) must teach or suggest all the claim limitations. M.P.E.P. §2143, citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As acknowledged by the Examiner, the prior art does not explicitly teach methods using a therapeutically effective dose of IL-2 in the range of about 0.5 to about 4.0 MIU/m^2 or a therapeutically effective dose of an antibody is in the range of about 1.0 to about 10.0 mg/kg. Nor can these dosages be readily extrapolated from the '227 and '726 patent as the Examiner suggests. The '227 patent suggests, and the '726 patent claims, an IL-2 dosage range of 3-3.75 x 10^6 U/kg to 7.5. x 10^6 U/kg of host weight, which is to be administered in combination with an immunotoxin in an amount of 25 to 500 μg/kg of host weight. As stated previously, for a 70 kg human, this is equivalent to 210-262.5 to 525 MIU IL-2, which is to be administered in combination with 0.025 to 0.5 mg/kg of the immunotoxin. The average person is about 1.7 m^2, thus the presently claimed IL-2 doses (about 0.5 MIU/m^2 to about 4.0 MIU/m^2) are equivalent to about 0.85 MIU to about 6.8 MIU. Thus, when extrapolated to human doses, the '227 and '726 patents teach combination therapy with an IL-2 dose that is at least about *31-fold higher* than the highest dose in the low IL-2 dosing range claimed in the present invention. Similarly, for a 20 g mouse, with a surface area of 0.004 m^2, the present invention teaches a dose of 0.002 MIU – 0.016 MIU, which is 30-fold less than the dose taught by the '227 and '726 patents (0.06 - 0.15 MIU).

Furthermore, the much higher IL-2 dose suggested in these two cited patents is combined with an immunotoxin dose that, in its highest value (i.e., 0.5 mg/kg immunotoxin, is only half that of the *lowest* anti-HER2 antibody dose (i.e., 1.0 mg/kg anti-HER2 antibody) suggested and claimed in the present invention. Applicants respectfully submit that the dosing regimen and doses taught by these two cited patents teach away from the IL-2/antibody dosing ranges of the presently claimed invention, and also fail to provide the requisite motivation or guidance to arrive at Applicants' claimed invention. Therefore, the supporting disclosures of the '227 and '726 patents would not render obvious the doses taught by the present invention. In addition,

neither '726 nor '227 teach that the treatment regimen can or should comprise intermediate-dose IL-2 pulsing.

The Examiner has stated that "the term extrapolate should be given only its plain meaning; *e.g.*, to estimate by projecting known data." Applicants submit that the dosing regimens of the instant application cannot be simply extrapolated from the '726 or '227 patents. Therefore, the '726 and '227 patents fail to teach or suggest all the claim limitations, and the Examiner has not met the *prima facie* burden for a rejection under either U.S.C. §102(b) or 35 U.S.C. §103(a).

For at least these reasons, Applicants respectfully request that the rejections under 35 U.S.C. §102(b) and §103(a) be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 12-62 stand rejected under 35 U.S.C. §103(a) as being unpatentable over either the '726 patent or the '227 patent "in view of Hank *et al.* (*Cancer Research* 50:5234-5239, 1990) and Keler *et al.* (*Cancer Research* 57:4008-4014, 1997), or Sliwkowski *et al.* (*Seminars in Oncology* 26:60-70, 1999) and Lewis *et al.* (*Cancer Immunology & Immunotherapy* 37:255-263, 1993), and further in view of Meropol *et al.* (*Cancer Immunology & Immunotherapy* 46:318-326, 1998)." These rejections are respectfully traversed.

As stated and discussed above, neither the '726 patent nor the '227 patent teach that a therapeutically effective dose of IL-2 is in the range of about 0.5 to about 4.0 MIU/m^2 or that a therapeutically effective dose of the anti-HER2 antibody is in the range of about 1.0 to about 10.0 mg/kg. The reference of Hank *et al.* does not remedy this inadequacy. Hank et al. teach a dose of 3 μg/ml antibody in an *in vitro* ADCC assay. Hank et al. fail to teach or suggest any therapeutic regimen combining IL-2 with antibodies. Further, no mention is made of effective *in vivo* antibody dosing. The Keler *et al.* reference also fails to teach or suggest the claimed combination of IL-2 with an anti-HER2 antibody or the dosing ranges recited in the pending claims.

Meropol *et al.* teach intermediate dose pulsing with IL-2 in patients with advanced malignancy. Although, Meropol *et al.* suggest such therapy might be combined with monoclonal antibodies recognizing tumor-associated antigens, in the absence of more guidance, such a

suggestion can at best be considered an invitation to experiment and as such is not a proper basis for an obviousness rejection.

No guidance is provided as to how to combine the teachings of the cited references and/or how to modify the cited references, to arrive at the protocols recited in the presently claimed invention. Even if one of skill in the art would be motivated to combine Hank *et al.* and Keler *et al.* with either the '726 patent or the '227 patent, and with Meropol *et al.*, which Applicants contend for reasons previously made of record that they would not, one would still not arrive at Applicants' invention, as none of these cited references teaches or even suggests the IL-2 and anti-HER2 antibody doses recited in Applicants' claimed invention. For at least these reasons, this rejection of the claims should be withdrawn.

In addition, the claims have been rejected under 35 U.S.C. §103(a) as being unpatentable over either the '726 patent or the '227 patent in view of Sliwkowski *et al.* and Lewis *et al.*, and further in view of Meropol *et al.*

As stated previously, neither the '726 patent nor the '227 patent teaches that a therapeutically effective dose of IL-2 is in the range of about 0.5 to about 4.0 MIU/m^2 or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg. Sliwkowski *et al.* and Lewis *et al.* are directed to specific disclosures regarding the efficacy of chimeric and humanized versions of the anti-HER2 murine 4D5 monoclonal antibody in ADCC assays and murine xenograft models. Sliwkowski *et al.* discuss combination efficacy studies with cytotoxic chemotherapeutic agents, but do not disclose IL-2 as a possible agent in these combination treatments. Lewis *et al.* discuss the differential response of various tumor cell lines that overexpress HER2 to anti-HER2 antibodies. Lewis *et al.* do not discuss treatment with IL-2. Therefore, any combination of the '726 patent or the '227 patent with Sliwkowski *et al.* and Lewis *et al.* would not result in the methods of the present invention.

Meropol *et al.* teach intermediate dose pulsing with IL-2 in patients with advanced malignancy. Although, Meropol *et al.* suggest such therapy with monoclonal antibodies, such a suggestion is merely an invitation to experiment since no guidance is provided as to how to combine the teachings of the cited references and/or how to modify the cited references to arrive at the protocols recited in the presently claimed invention.

Applicants reiterate their position that the Examiner's rejections in view of the various combinations of Hank *et al.*, Keler *et al.*, Silwkowski *et al.*, Lewis *et al.*, or Meropol *et al.* with the '726 patent or the '227 patent are based upon impermissible hindsight reasoning. The '726 patent or the '227 patent provide no guidance for "extrapolating" their teachings to arrive at Applicants' claimed invention. The requisite guidance is not provided by the combination of these two cited patents with any of the other cited references. Unless the Examiner shows that at the time the invention was made there was something more than a mere suggestion of success based upon the cited references, obviousness has not been demonstrated.

For all of the reasons made of record, and reiterated herein, Applicants respectfully submit that the cited references do not teach or even suggest the claimed invention. As such, this rejection of the claims should be withdrawn.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 12-27 and 29-62 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In particular, the Final Office Action alleges that the designation "IL-2" or "human IL-2" as the sole means of identifying the polypeptide to which said variant of "said IL-2" has at least 70% amino acid sequence identity renders the claims indefinite because the "same designation may be used to define completely distinct polypeptides" and "because a comparison cannot be made without a disclosure of the specific reference to which said comparison is made, the metes and bounds of the subject matter that Applicant regards as the invention cannot be determined (Final Office Action, pages 27-28).

While Applicants disagree that the designation "IL-2" is indefinite, claims 12, 16, 17, and 42 have been amended to recite the sequence of SEQ ID NO:1. Therefore, this rejection should be withdrawn.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

Amy Hessler
Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Tel: (510) 923-3833
Fax: (510) 655-3542

Respectfully submitted,

Date: August 5, 2005

By: Jenny Buchbinder

Jenny Buchbinder, Ph.D.
Registration No. 48,588
(650) 354-3383

CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097